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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US97/02793 <b>(22) International Filing Date:</b> 21 February 1997 (21.02.97) <b>(30) Priority Data:</b> 08/630,065 12 April 1996 (12.04.96) US <b>(71) Applicant (for all designated States except US):</b> FLEMINGTON PHARMACEUTICAL CORPORATION [US/US]; 43 Emery Avenue, Flemington, NJ 08822 (US). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> DUGGER, Harry, A., III [US/US]; 548 Sargentville Road, Flemington, NJ 08822 (US). <b>(74) Agent:</b> BEHR, Omri, M.; 325 Pierson Avenue, Edison, NJ 08837 (US).			<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> BUCCAL POLAR SPRAY OR CAPSULE			
<b>(57) Abstract</b>  A buccal aerosol spray or capsule using a polar solvent has now been developed which provides biologically active compounds for rapid absorption through the oral mucosa, resulting in fast onset of effect. The buccal aerosol spray of the invention comprises: polar solvent 5-50 %, active compound 0.0025-40 %, flavoring agent 0.05-5%. The soft bite gelatin capsule of the invention comprises as fill composition: polar solvent 75-99 %, emulsifier 0-20 %, active compound 0.0003-35 %, and flavoring agent 0.05-60 %.			

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**TITLE OF THE INVENTION**  
**BUCCAL POLAR SPRAY OR CAPSULE**

**BACKGROUND OF THE INVENTION**

5        It is known that certain biologically active compounds are better absorbed through the oral mucosa than through other routes of administration, such as through the stomach or intestine. However, formulations suitable for such administration by these latter routes present their own problems. For example, the biologically active compound must  
10 be compatible with the other components of the composition such as propellants, solvents, etc. Many such formulations have been proposed. For example, U.S.P. 4,689,233, Dvorsky *et al.*, describes a soft gelatin capsule for the administration of the anti-coronary drug nifedipine dissolved in a mixture of polyether alcohols. U.S.P. 4,755,389, Jones *et al.*,  
15 describes a hard gelatin chewable capsule containing nifedipine. A chewable gelatin capsule containing a solution or dispersion of a drug is described in U.S.P. 4,935,243, Borkan *et al.* U.S.P. 4,919,919, Aouda *et al.*, and U.S.P. 5,370,862, Klokke-Bethke, describe a nitroglycerin spray for administration to the oral mucosa comprising nitroglycerin, ethanol, and  
20 other components. An orally administered pump spray is described by Cholcha in U.S.P. 5,186,925. Aerosol compositions containing a hydrocarbon propellant and a drug for administration to a mucosal surface are described in U.K. 2,082,457, Su, U.S.P. 3,155,574, Silson *et al.*, U.S.P. 5,011,678, Wang *et al.*, and by Parnell in U.S.P. 5,128,132. It should be  
25 noted that these references discuss bioavailability of solutions by inhalation rather than through the membranes to which they are administered.

**SUMMARY OF THE INVENTION**

A buccal aerosol spray or soft bite gelatin capsule using a polar  
30 solvent has now been developed which provides biologically active compounds for rapid absorption through the oral mucosa, resulting in fast onset

of effect.

The buccal aerosol spray compositions of the present invention, for transmucosal administration of a pharmacologically active compound soluble  
5 in a pharmacologically acceptable polar solvent comprising in weight% of total composition: polar solvent 75-99.8%, active compound 0.0025-40%, suitably additionally comprising, by weight of total composition a flavoring agent 0.05-5%. Preferably the composition comprises: polar solvent 75-99%, active compound 0.025-20%, flavoring agent 0.1-2.5%; most  
10 suitably polar solvent 75-98%, active compound 0.125-12.5%, flavoring agent 0.1-2.5%.

The soft bite gelatin capsules of the present invention for trans-mucosal administration of a pharmacologically active compound, at least  
15 partially soluble in a pharmacologically acceptable polar solvent, having charged thereto a composition comprising in weight % of total composition: polar solvent 40-99.8%, emulsifier 0-20%, active compound 0.0003-35%, provided that said composition contains less than 10% of water, suitably additionally comprising, by weight of the composition: flavoring agent  
20 0.05-60%. Preferably, the soft bite gelatin capsule comprises: polar solvent 50-99.8%, emulsifier 0-15%, active compound 0.0003-26%, flavoring agent 0.5-55%; most suitably: polar solvent 70-99.5%, emulsifier 0-10%, active compound 0.015-24.0%, flavoring agent 0.1-50%.

25 It is an object of the invention to coat the mucosal membranes either with extremely fine droplets of spray containing the active compounds or a solution or paste thereof from bite capsules.

It is also an object of the invention to administer to a mammalian need  
30 of same preferably man, a predetermined amount of a biologically active compound by this method or from a soft gelatin bite capsule.

A further object is a pump spray container containing a composition of the spray formulation, and a metered valve suitable for releasing from said container a predetermined amount of said composition.

- 5           The solvent is a low molecular weight, pharmacologically acceptable alcohol, water, glycerine or polyethylene glycol or mixtures thereof.

A further object is a soft gelatin bite capsule containing a composition as set forth above. The formulation may be in the form of a viscous solution or paste containing the active compounds. Although solutions are preferred, paste fills may also be used where the active compound is not soluble or only partially soluble in the solvent of choice. Where water is used to form part of the solvent or paste composition, it should not exceed 10% thereof. (All percentages herein are by weight unless otherwise indicated.)

The polar solvent is chosen such that it is compatible with the gelatin shell and the active compound. The solvent preferably dissolves the active compound. However, other components wherein the active compound is not soluble or only slightly soluble may be used and will form a paste fill.

Soft gelatin capsules are well known in the art. See, for example, U.S.P. 4,935,243, Borkan et al., which is incorporated herein by reference for its teaching of such capsules. The capsules of the present invention are intended to be bitten into to release the low viscosity solution or paste therein, which will then coat the buccal mucosa with the active compounds. Typical capsules, which are swallowed whole or bitten and then swallowed, deliver the active compounds the stomach, which results in significant lag time before maximum blood levels can be achieved or subject the compound to large first pass effect. Because of the enhanced absorption of the compounds through the oral mucosa and no chance of a first pass effect,

use of the bite capsules of the invention will eliminate much of the lag time, resulting in hastened onset of biological effect. The shell of a soft gelatin capsule of the invention may comprise, for example: gelatine 50-75%, glycerine 20-30%, colorants 0.5-1.5%, water 5-10%, and sorbitol 2-10%.

5

The spray compositions of the invention are intended to be administered from a pump spray.

#### BRIEF DESCRIPTION OF THE DRAWING

10 The figure is a schematic diagram showing routes of absorption and processing of pharmacologically active substances in a mammalian system.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred active compounds of the present invention are nicotine,  
15 clemastine, testosterone, estradiol, progesterone, fluoxetine, and piroxicam in their nonionized form or as the free base of the pharmaceutically acceptable salts thereof (provided, for the aerosol or spray compositions, they are soluble in the spray solvent). These compounds are soluble in the non-polar solvents of the invention at useful concentrations or can be  
20 prepared as pastes at useful concentrations. These concentrations may be less than the standard accepted dose for these compounds since there is enhanced absorption of the compounds through the oral mucosa. This aspect of the invention is especially important when there is a large (40-99.99%) First pass effect.

25

As solvents for the sprays there may be used low molecular weight polyethyleneglycols (PEG) of 400-1000 Mw (preferably 400-600). Low molecular weight alcohols and polyols, such as glycerin may also be present and water may also be used.

30

Suitable solvents for the capsules include low molecular weight polyethylen glycols (PEG) of 400-1000 Mw (preferably 400-600). Low



molecular weight alcohols and polyols, such as glycerin may also be present and water may also be used. However, these should only be used sparingly in the bite capsule compositions as they may migrate into the gelatin shell and weaken it.

5

It is expected that some glycerin and water used to make the gelatin shell will migrate from the shell to the fill during the curing of the shell. Likewise, there may be some migration of components from the fill to the shell during curing and even throughout the shelf-life of the capsule.

10 Therefore, the values given herein are for the compositions as prepared, it being within the scope of the invention that minor variations will occur.

The preferred flavoring agents are synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, chocolate, sweeteners (sugars, 15 aspartame, saccharin, etc.), and combinations thereof.

The active substances include the active compounds selected from the group consisting of alkaloids, anti histamines, steroid hormones, non-steroidal anti-inflammatories, analgesics and anti-depressants, benzo- 20 diazepines, such as tmezepam.

Clemastine hydrogen fumarate is a known (Tavist®, Sandoz) anti-histamine. Both the spray and capsule of the invention advantageously coat the oral mucosa with an immediately available dose of clemastine which can be rapidly absorbed. This is highly desirable, as during an acute asthma 25 attack.

Nicotine is a component of tobacco products which is considered addictive. Smokers wishing to stop smoking have a dual problem. First, is the addictive properties of nicotine itself. Second, is that the habit is 30 associated with smoking activities, i.e., puffing, inhaling, etc. Both the spray and capsule of the invention dissociate these two problems. By

presenting nicotine in a form which can be readily absorbed, the spray and capsule allow the smoker to temporarily continue nicotine use but terminate smoking. Once the habit of smoking is stopped, the former smoker can then be weaned off nicotine use, as by less frequent use and/or by use of  
5 a lower concentration spray or capsule. Advantageously, during this regimen, the user is exposed to none of the carcinogens present in tobacco smoke.

Testosterone is a hormone produced by gonadal cells. Testosterone,  
10 especially the esters thereof (e.g., acetate, propionate, enanthate, and cypionate), is used in the treatment of hypogonadism.

Estradiol is an estrogen steroid secreted from the ovaries. Estradiol, especially the esters thereof (e.g., diacetate, and benzoate), is used as  
15 estrogen replacement therapy, especially in post-menopausal women.

Progesterone is a hormone produced by the corpus luteum. Fluoxetine is an antidepressant also known as Prozac. Piroxicam is a known (Feldene®, Pfizer) anti-inflammatory.

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20

The formulations of the present invention comprise an active compound or a pharmaceutically acceptable salt thereof. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including organic and  
25 inorganic acids or bases.

When an active compound of the present invention is acidic, salts may be prepared from pharmaceutically acceptable non-toxic bases. Salts derived from all stable forms of inorganic bases include aluminum,  
30 ammonium, calcium, copper, iron, lithium, magnesium, manganese, potassium, sodium, zinc, etc. Particularly preferred are the ammonium,

calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, isopropylamine, lysine, methylglucosamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purine, theobromine, triethylamine, trimethylamine, tripropylamine, etc.

When an active compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, etc. Particularly preferred are citric, hydrobromic, maleic, phosphoric, sulfuric, and tartaric acids.

In the discussion of methods of treatment herein, reference to the active compounds is meant to also include the pharmaceutically acceptable salts thereof. While certain formulations are set forth herein, the actual amounts to be administered to the mammal or man in need of same are to be determined by the treating physician.

The invention is further defined by reference to the following examples, which are intended to be illustrative and not limiting.

### EXAMPLE 1

#### 5 Clemastine Spray

A spray of the invention comprises the following formulation:

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
Polar solvent	75-99%	90-99%	97-99%
Clemastine fumarate	0.12-12.5%	0.25-7.25%	0.25-6.5%
10 Flavoring agent	0.05-5%	0.1-2.5%	0.2-2%

It is particularly preferred to formulate the spray delivering 1.34mg/activation:

	<u>Amount</u>
15 Polar solvent:	
Ethanol	66%
Water	31%
Clemastine fumarate	2.8%
Peppermint Oil	0.2%

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20

### EXAMPLE 2

#### Nicotine Spray

A spray of the invention comprises the following formulation:

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
25 Polar solvent	75-99.8%	96-99.8%	96-99.8%
Nicotine	0.0125-10%	0.125-2.5%	0.2-1.15%
Flavoring agent	0.05-5%	0.1-2.5%	0.2-2.0%

It is particularly preferred to formulate the spray delivering 30 .0.5mg/activation:

	<u>Amount</u>
Polar solvent:	
Ethanol	49.37%
Water	49.37%
5 Nicotine	1.06%
Peppermint Oil	0.2%

## EXAMPLE 3

## Nicotine Sulfate

10 A spray of the invention comprises the following formulation:

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
Polar solvent	75-99.8%	96-99.8%	96-99.8%
Nicotine Sulfate	0.0125-10%	0.125-2.5%	0.2-2.0%
Flavoring agent	0.05-5%	0.1-2.5%	1-2%

15

It is particularly preferred to formulate the spray for 0.5mg of nicotine sulfate:

	<u>Amount</u>
Polar solvent:	
20 Ethanol	9.84%
Water	88.9%
Nicotine Sulfate	1.06%
Peppermint Oil	0.2%

## EXAMPLE 4

## Fluoxetine Hydrochloride Spray

A spray of the invention comprises the following formulation:

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
5 Polar solvent	75-99%	75-98%	75-95%
Fluoxetine Hydrochloride	0.125-25%	2.5-20%	5-12.5%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.0%

10

It is particularly preferred to formulate the spray delivering 5mg/activation:

	<u>Amount</u>
Polar solvent:	
15 Ethanol	48.4%
Water	10.0%
Polyethyleneglycol	30.0%
Fluoxetine HCl	10.6%
Oil of Orange	1.0%

20

## EXAMPLE 5

## Testosterone Spray Delivering 3mg/Activation

A spray of the invention comprises the following formulation:

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
25 Polar Solvent	55-99%	75-95%	85-93%
Testosterone	0.12-10%	0.25-7.5%	0.25-6.5%
Flavoring Agent	0.05-3%	0.1-2.5%	0.1-2.5%

It is particularly preferred to formulate the spray:

	<u>Amount</u>
Polar Solvent:	
Water	10%
5 Polyethyleneglycol	65%
Ethanol	16.6%
Testosterone	6.4%
Orange Aroma	1.0%
Oil of Citrus	1.0%
10	

#### EXAMPLE 6

Estradiol Spray Delivering 0.1mg/Activation

A spray of the invention comprises the following formulation:

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
15 Polar Solvent	75-99%	75-95%	85-99%
Estradiol	0.0025-2.5%	0.025-1.5%	0.125-1.0%
Flavoring Agent	0.05-3%	0.1-2.5%	1-2%

It is particularly preferred to formulate the spray:

	<u>Amount</u>
Polar Solvent:	
Water	10%
Polyethyleneglycol	75%
Ethanol	13.79%
25 Estradiol	0.21%
Peppermint	1.0%

**EXAMPLE 7****Progesterone Spray Delivering 0.32mg/Activation**

A spray of the invention comprises the following formulation:

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
5 Propellant	55-99%	75-99.8%	85-99.5%
Progesterone	0.12-10%	0.25-6.25%	0.25-1%
Flavoring Agent	0.05-3%	0.1-2.5%	1-2%

It is particularly preferred to formulate the spray:

10	<u>Amount</u>
	<b>Polar Solvent:</b>
	Water 10%
	Polyethyleneglycol 75%
	Ethanol 13.32%
15	Progesterone 0.68%
	Peppermint 1.0%

**EXAMPLE 8****Clemastine Bite Capsule**

20 A bite capsule of the invention comprises the following fill formulation:

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
Polar solvent	55-99%	66-97%	85-99.5%
Emulsifier	0-20%	0-15%	0-10%
25 Clemastine fumarate	0.1-4%	0.03-3%	0.04-1.5%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%



It is particularly preferred to formulate the composition fill for a 1.34mg capsule:

	<u>Amount</u>
Polar Solvent:	
5 Polyethyleneglycol	89.6% %
Water	5.3%
Glycerine	4.4%
Clemastine fumarate	0.50%
Peppermint Oil	0.1%
10 Saccharine	0.1%

#### EXAMPLE 9

##### Testosterone Bite Capsule

A bite capsule of the invention comprises the following fill  
15 formulation:

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
Polar solvent	55-99%	66-97%	85-99.5%
Emulsifier/wetting agents	0-20%	0-15%	0-10%
20 Testosterone*	0.01-3.7%	0.4-3%	0.7-2%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%

\*or esters thereof, preferably, the acetate, propionate, and enanthate esters

It is particularly preferred to formulate the fill composition for the 5mg capsule:

	<u>Amount</u>
Polar solvent:	
5 Polyethyleneglycol	85.0%
Glycerine	6.15%
Lecithin	6.0%
Testosterone	1.85%
Peppermint Oil	1.0%

10

## EXAMPLE 10

## Estradiol Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

15	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
Polar solvent	75-99%	75-99.8%	85-99.5%
Emulsifier/wetting agents	0-20%	0-15%	0-10%
Estradiol*	0.0003-2%	0.003-0.75%	0.02-0.2%
20 Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%

\*or esters thereof, preferably, the diacetate and benzoate esters

It is particularly preferred to formulate the fill composition for a 0.5mg capsule:

25	<u>Amount</u>
Polar solvent:	
Polyethyleneglycol	85%
Glycerine	8.82%
Lecithin	5.0%
30 Estradiol	0.18%
Oil of Peppermint	1.0%

## EXAMPLE 11

## Progesterone Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

5		<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
	Polar solvent	75-99.8%	75-98.8%	85-99.5%
	Emulsifier/wetting agents	0-20%	0-15%	0-10%
	Progesterone	0.0003-4%	0.0003-3%	0.75-2%
10	Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%

It is particularly preferred to formulate the fill formulation for a 3mg capsule:

	<u>Amount</u>
15 Polar solvent:	
Polyethyleneglycol	85%
Glycerine	7.89%
Lecithin	5.0%
Progesterone	1.11%
20 Oil of Peppermint	1.0%

## EXAMPLE 12

## Fluoxetine Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

25		<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
	Polar solvent	75-99.8%	75-99.8%	85-99.5%
	Emulsifier/wetting agents	0-20%	0-15%	0-10%
30	Fluoxetine HCl	0.2-9.25%	0.4-6%	0.75-4%
	Flavoring agent	0.05-5%	0.1-2.5%	0.5-3%

It is particularly preferred to formulate the fill formulation for a 5mg capsule:

	<u>Amount</u>
Polar solvent:	
5 Polyethyleneglycol	85%
Glycerine	7.15%
Lecithin	5.0%
Fluoxetine HCl	1.85%
Oil of Peppermint	1.0%

10

## EXAMPLE 13

## Piroxicam Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

15	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
Polar solvent	75-99.8%	75-99.8%	95-99.5%
Emulsifier/wetting agents	0-20%	0-15%	0-10%
Piroxicam	0.02-9.25%	0.4-4%	0.75-4%
20 Flavoring agent	0.05-5%	0.1-4.5%	0.5-3%

It is particularly preferred to formulate the fill formulation for a 5mg capsule:

	<u>Amount</u>
25 Polar solvent:	
Polyethyleneglycol	85%
Glycerine	7.5%
Lecithin	5.0%
Piroxicam	1.85%
30 Oil of Peppermint	1.0%

## EXAMPLE 14

## Clemastine Fumarate with Phenylpropanolamine Hydrochloride Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
5 Polar solvent	40-99%	50-98%	70-98%
Emulsifier	0-20%	0-15%	0-10%
Clemastine fumarate	0.01-1.85%	0.03-0.74%	0.05-0.185%
10 Phenylpropanolamine HCl	1-30%	1.5-20%	1.8-10%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%

15

It is particularly preferred to formulate the composition fill for a clemastine 1.34mg/25mg phenylpropanolamine capsule:

	<u>Amount</u>
Polar Solvent:	
20 Polyethyleneglycol	78.73%
Water	5.3%
Glycerine	4.4%
Clemastine fumarate	0.5%
Phenylpropanolamine HCl	9.2%
25 Saccharine	0.37%
Peppermint Oil	1.5%

## EXAMPLE 15

## Clemastine/Pseudoephedrine Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
5			
Polar solvent	40-99%	60-95%	70-90%
Emulsifier	0-20%	0-15%	0-10%
Clemastine fumarate	0.01-1.85%	0.03-0.74%	0.05-0.1.85%
10			
Pseudoephedrine HCl	3-30%	5-25%	10-23%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%

15

It is particularly preferred to formulate the composition fill for a 1.34mg clemastine fumarate/60mg pseudoephedrine HCl capsule:

	<u>Amount</u>
Polar Solvent:	
20 Polyethyleneglycol	65.71%%
Water	5.30%
Glycerine	4.40%
Clemastine fumarate	0.50%
Pseudoephedrine HCl	22.22%
25 Peppermint Oil	1.5%
Saccharine	0.37%

## EXAMPLE 16

## Nicotine 0.5mg Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

5		<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
	Polar solvent	30-99.8%	35-99.8%	40-99.5%
	Emulsifier/wetting agents	0-20%	0-15%	0-10%
	Nicotine*	0.018-0.74%	0.037-0.37%	0.37-0.20%
10	Flavoring agent	0.05-60%	0.1-55%	0.5-50%
	* or as nicotine sulfate			

It is particularly preferred to formulate the fill for a 0.5mg capsule:

	<u>Amount</u>
Polar Solvent:	
15 Polyethyleneglycol	89.6%%
Water	5.5%
Glycerine	4.40%
Peppermint Oil	0.1%
Na Saccharine	0.1%
20 Nicotine	0.185%

**WHAT IS CLAIMED IS:**

1. A buccal aerosol spray composition for transmucosal administration of a pharmacologically active compound soluble in a  
5 pharmacologically acceptable polar solvent comprising in weight % of total composition: polar solvent 75-99.8%, active compound 0.0025-40%.

2. The composition of claim 1 additionally comprising, by weight of total composition: flavoring agent 0.05-5%.

10

3. The composition of claim 1 comprising: polar solvent 75-99%, active compound 0.025-20%, flavoring agent 0.1-2.5%.

4. The composition of claim 1 comprising: polar solvent 75-98%,  
15 active compound 0.125-12.5%, flavoring agent 0.1-2.5%.

5. The composition of Claim 1 wherein the solvent is a selected from the group consisting of C<sub>7-18</sub> hydrocarbons of a linear or branched configuration, the alcohols thereof, the fatty acid esters of said alcohols.

20

6. The composition of Claim 1 wherein the solvent is miglyol.

7. The composition of Claim 1 wherein the active compound is selected from the group consisting of alkaloids, non-steroidal anti-  
25 inflammatories, analgesics, anti-histamines, steroid hormones, benzo-diazepams, and anti-depressants.

8. The composition of Claim 7 wherein the active compound is selected from the group consisting of nicotine, clemastine, testosterone,  
30 estradiol, progesterone, t mazepam, fluoxetine, and piroxicam in their nonionized form or as the free base of the pharmaceutically acceptable salts



thereof.

9. The composition of Claim 2 wherein the flavoring agents are selected from the group consisting of synthetic or natural oil of peppermint,  
5 oil of spearmint, citrus oil, fruit flavors, sweeteners and combinations thereof.

10. The composition of Claim 2 of the formulation: polar solvent 75-99%, clemastine 0.12-10%, flavoring agent 0.05-5%.

10

11. The composition of Claim 2 of the formulation: polar solvent 75-99%, nicotine 0.0125-10%, flavoring agent 0.05-5%.

12. A method of administering a pharmacologically active  
15 compound to a mammal in need of same, by spraying the oral mucosa of said mammal with a composition of claim 1.

13. The method of claim 12 wherein the amount of spray administered is predetermined.

20

14. A soft bite gelatin capsule for transmucosal administration of a pharmacologically active compound, at least partially soluble in a pharmacologically acceptable polar solvent, having charged thereto a fill composition comprising in weight % of total fill composition: polar solvent  
25 50-99.8%, emulsifier 0-20%, active compound 0.0003-26%, provided that said composition contains less than 10% of water.

15. The capsule of claim 14 additionally comprising, by weight of the fill composition: flavoring agent 0.05-60%.

30

16. The soft bite gelatin capsule of Claim 14 comprising as the fill composition: polar solvent 50-99.8%, emulsifier 0-15%, active compound 0.0003-26%, flavoring agent 0.1-50%.

5 17. The soft bite gelatin capsule of Claim 14 comprising as the fill composition: polar solvent 70-99.5%, emulsifier 0-10%, active compound 0.015- 24.0%, flavoring agent 0.1-50%.

18. The capsule of Claim 14 wherein the solvent is selected from  
10 the group consisting of low molecular weight polyethyleneglycols (PEG) of 400-1000 MW, (C<sub>2</sub>-C<sub>24</sub>) fatty acid (C<sub>2</sub>-C<sub>8</sub>) esters, C<sub>2</sub>-C<sub>8</sub> mono- and poly-alcohols, C<sub>7</sub>-C<sub>18</sub> hydrocarbons of a linear or branched configuration, the alcohols thereof, and the fatty acid esters of said alcohols.

15 19 The capsule of Claim 14 wherein the solvent is selected from low molecular weight polyethyleneglycols (PEG) of 400-600 MW, (C<sub>2</sub>-C<sub>24</sub>) fatty acid (C<sub>2</sub>-C<sub>8</sub>) esters and the triglycerides of said fatty acids.

20. The composition of Claim 14 wherein the active compound is  
20 selected from the group consisting of alkaloids, non-steroidal anti-inflammatories, analgesics, anti-histamines, steroid hormones, benzodiazepams, and anti-depressants.

21. The capsule of Claim 14 wherein the active compound is  
25 nicotine, clemastine, testosterone, estradiol, progesterone, fluoxetine, or piroxicam in their nonionized form or as the free base of the pharmaceutically acceptable salts thereof.

22. Th capsule of Claim 14 wher in the flavoring ag nts ar  
30 synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, or sweeteners and combinations thereof.

23. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 75-99%, emulsifier 0-20%, clemastine fumarate 0.01-4%, flavoring agent 0.05-5%.

5 24. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 55-99%, emulsifier 0-20%, a member selected from the group consisting of testosterone and the esters thereof 0.01-4%, flavoring agent 0.05-5%.

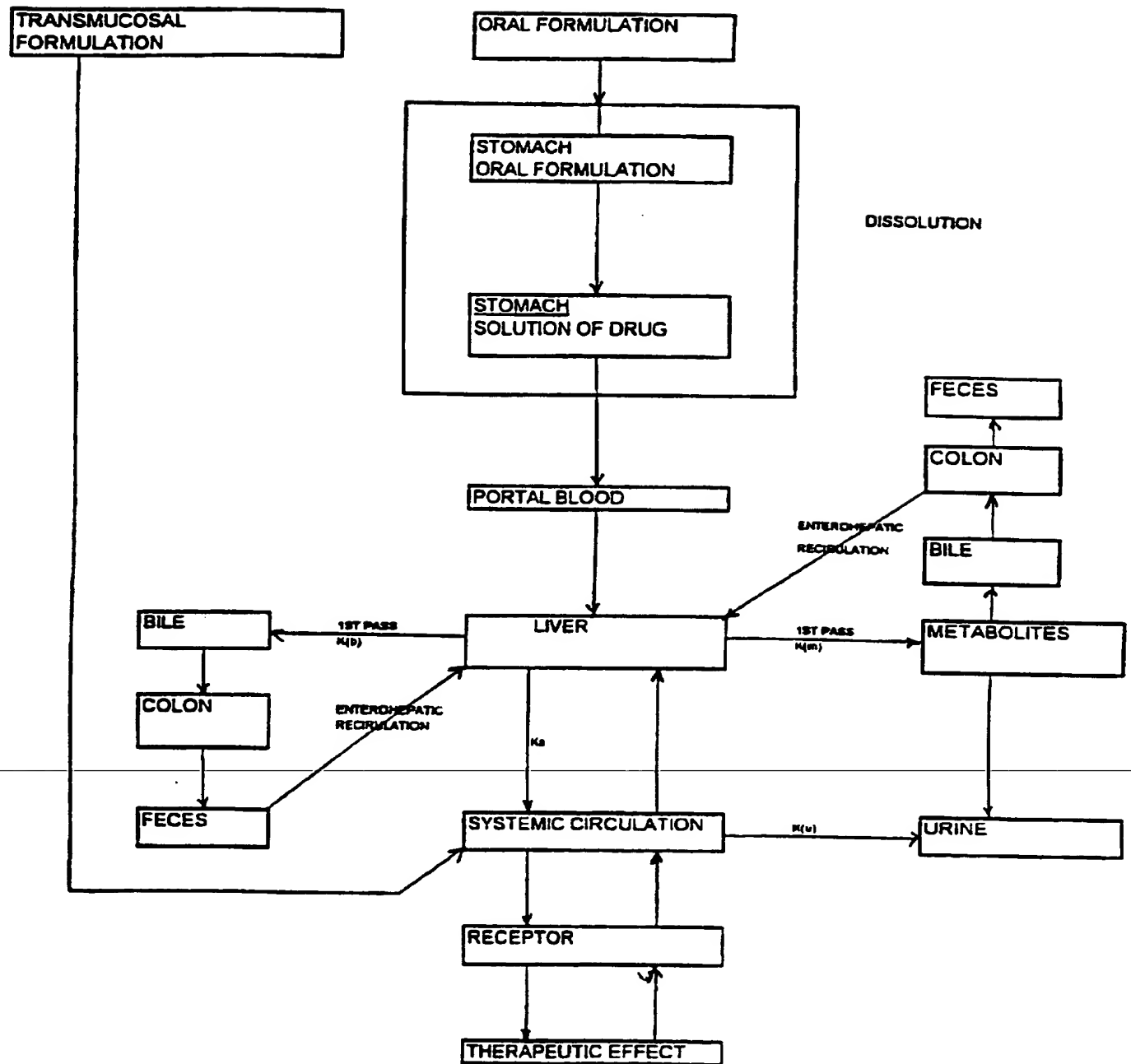
10 25. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 65-99%, emulsifier 0-20%, estradiol 0.0003-2%, flavoring agent 0.05-5%.

15 26. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 75-99.8%, emulsifier 0-20%, progesterone 0.0003-4%, flavoring agent 0.05-5%.

20 27. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 75-99.8%, emulsifier 0-20%, fluoxetine HCl 0.02-9.5%, flavoring agent 0.05-5%.

28. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 75-99.8%, emulsifier 0-20%, piroxicam 0.02-9.5%, flavoring agent 0.05-5%.

1/1



$$K(e) = K(m) + K(b) + K(u)$$

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification<sup>6</sup>:</b> <b>A61K 9/00, 9/12, 47/10, 9/48</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 97/38662</b> <b>(43) International Publication Date:</b> 23 October 1997 (23.10.97)
<b>(21) International Application Number:</b> PCT/US97/02793 <b>(22) International Filing Date:</b> 21 February 1997 (21.02.97) <b>(30) Priority Data:</b> 08/630,065 12 April 1996 (12.04.96) US <b>(71) Applicant (for all designated States except US):</b> FLEMINGTON PHARMACEUTICAL CORPORATION [US/US]; 43 Emery Avenue, Flemington, NJ 08822 (US). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> DUGGER, Harry, A., III [US/US]; 548 Sargentville Road, Flemington, NJ 08822 (US). <b>(74) Agent:</b> BEHR, Omri, M.; 325 Pierson Avenue, Edison, NJ 08837 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>  <b>(88) Date of publication of the international search report:</b> 12 February 1998 (12.02.98)
<b>(54) Title:</b> BUCCAL POLAR SPRAY OR CAPSULE  <b>(57) Abstract</b> <p>A buccal aerosol spray or capsule using a polar solvent has now been developed which provides biologically active compounds for rapid absorption through the oral mucosa, resulting in fast onset of effect. The buccal aerosol spray of the invention comprises: polar solvent 75-99,8 % compound 0.0025-40 %, flavoring agent 0.05-5 %. The soft bite gelatin capsule of the invention comprises as comprising as fill composition: polar solvent 50-99,8 %, emulsifier 0-20 %, active compound 0.0003-26 %, and flavoring agent 0.05-60 %.</p>		

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# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/93/02793

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K9/00 A61K9/12 A61K47/10 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 39 22 650 A (EGYT GYOGYSZERVEGYESZETI GYAR) 11 January 1990 see page 5 - page 7; claims 1-9 ---	1-13
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

6 November 1997

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# INTERNATIONAL SEARCH REPORT

International application No.

US 97/02793

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
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2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
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## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1 - 13  
14 - 28

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
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Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
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Information on patent family members

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